A Phase II Randomized Trial of Recombinant Fowlpox that Expresses PSA in Patients with Adenocarcinoma of the Prostate.

Vaccinia virus has been used as an immunotherapy vaccine to produce cellular and humoral responses to tumor associated antigens in human cancer. Recombinant vaccinia (rV) virus vectors engineered to contain genomic sequences to carcinoembryonic antigen (CEA), prostate specific antigen (PSA), and MUC1/ interleukin-2 (IL-2) have been safely administered to patients with advanced cancer with the development of specific cytotoxic T lymphocytes (CTLs) against the target antigen with evidence clinical disease stabilization. The epitopes of amino acid (aa) 141-150 and 154-163 of PSA elicit a CTL response capable of lysing prostatic carcinoma cell lines in vitro, including those infected with rV-PSA. rV-PSA was administered as 3 consecutive monthly doses to 33 men with a rising PSA after radical prostatectomy, radiation therapy, both, or metastatic disease at presentation. Dose levels were 2.65×10^6, 2.65×10^7, and 2.65×10^8 plaque forming units (pfu). The last 10 patients also received GM-CSF, 250ug/m^2as an immunostimulatory adjunct. No patient experienced any virus effects beyond grade I cutaneous toxicity. Pustule formation occurred after the first dose in all 28 men who received $\geq 2.65 \times 10^7$ pfu. GM-CSF was associated with fevers and myalgias, $\leq$ Grade 2 in 9/10 patients. Patients were removed from protocol for clinical progression or 3 monthly rises in PSA > 50% of baseline. Three of 23 men treated with rV-PSA alone remain on study $12\text{-}22^+$ months with stable disease. All 10 patients treated with rV-PSA & GM-CSF remain on study with $1\text{-}4^+$ m of follow-up, including some men with continuously falling serum PSA levels. Immunologic studies are ongoing at this time. rV-PSA is safe, can elicit a clinical immune reaction (pustule), and some patients remain without evidence of clinical progression for up to 22^+ months.

Fowl pox is (FPV) an avian pox virus which does not replicate in human cells. It can express a large number of recombinant genes and stimulate both cellular and humoral immunity. There is little if any cross reactivity with vaccinia viruses; thus individuals previously vaccinated with vaccinia will not have pre-existing immunity to FPV. Studies using rFPV containing the human melanoma tumor antigens MART-1 (rF-MART-1) and gp100 (rF-gp100) as an intramuscular injection have recently been conducted at the NCI. No significant toxicity was reported. Studies against a β-gal expressing syngeneic murine tumor combining rV-β-gal and rF-β-gal showed superior survival to the sequential administration of both viruses than to either one alone.

In this randomized Phase II trial, an initial cohorts of patients will receive three monthly injections of 1.5×10^8 and 1.5×10^9 plaque forming units (pfu) of rF-PSA. Escalations will proceed in the absence of dose limiting toxicity. Patients will monitored for clinical response and serologic response (PSA). Immunologic response will be measured by the titer of CTLs produced with serial vaccinations. When a safe dose has been established, additional patients will be randomly allocated to one of 2 sequences of rF-PSA followed by rV-PSA (2.65×10^8 pfu) or the reverse. Immunologic responses and serum PSA will be followed as will time to disease progression-either a greater than 50% rise in serum PSA for three consecutive months or the development of clinical disease progression.